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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,734	07/14/2003	Gregory Gregoriadis	G0365.0365/P0365	3606

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/617,734	Applicant(s) GREGORIADIS, GREGORY	
	Examiner Richard Schnizer, Ph. D.	Art Unit 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 December 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *13 December 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3,6-20,22,25-31 and 34-36*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claim 17-20, 22, and 25-32 under 35 USC 112, second paragraph.

Response to Arguments

Applicant's arguments filed 12/15/06 have been fully considered but they are not persuasive for the reasons of record in the Action mailed 6/13/06. Applicant reviews the Felgner reference at pages 10-11 of the response, and concludes that there is no teaching or suggestion in Felgner of cationic liposomes in which polynucleotides encoding immunogens are entrapped in the intravesicular space. The Examiner disagrees. The reference need not disclose applicant's invention in one sentence or even in one paragraph. The reference must be considered as a whole to determine what it fairly teaches. Felgner clearly states that the invention embraces delivery of nucleic acids that express immunogens in the paragraph bridging columns 7 and 8. Felgner also clearly indicates that therapeutic agents and "biologically active agents" include polynucleotides that can express proteins (see e.g. column 7, lines 49-56 and column 8, lines 60-65). Further, Felgner clearly teaches that the lipids of the invention may be used to form liposomes, and that the liposomes may encapsulate bioactive agents. See column 15, lines 7-25. There is no reason at all to assume that these active agents do not include nucleic acids encoding immunogens.

Applicant also asserts that Felgner fails to teach any in vivo results, noting that all experiments in Felgner were carried out in cell lines in vitro. However Applicant does not set forth any analysis that would lead one to the conclusion that the disclosure of Felgner was not enabling for the induction of an immune response. Furthermore, the Weiner and Liu references provide ample teachings to support this enablement.

Applicant argues at page 12 of the response that the Kirby reference fails to overcome the alleged deficiencies of Felgner because Kirby does not teach DNA vaccines. This is unpersuasive because Kirby was not relied upon to teach DNA vaccines, Kirby was relied upon to teach a dehydration-rehydration method of encapsulating solutes such as DNA into liposomes that is a simple method which provides excellent encapsulation yields while using mild conditions. The method also results in a greater proportion of oligo- and multilamellar vesicles which decrease the rate of loss of entrapped solutes (see paragraph bridging pages 982, and 983) and would be expected to exclude nucleases with greater success than unilamellar vesicles, thereby increasing the stability of the encapsulated nucleic acid.

Applicant asserts that the best argument for combining Kirby with Felgner is that it would have been obvious to try the combination. In support, Applicant argues that Kirby does not teach DNA vaccines, taught entrapment of E. coli genomic DNA, did not show functionality of entrapped DNA, and did not teach in vivo delivery of DNA. This is unpersuasive because Weiner and Liu each provide working examples of DNA vaccines, and Weiner suggested use of liposomes to deliver these vaccines. There is no reason of record to believe that entrapment of nucleic acids in liposomes would eliminate DNA expression construct activity in vivo. On the contrary, one of ordinary skill in the art would reasonably expect to decrease the susceptibility of the entrapped nucleic acids to nucleases, thereby increasing the stability of the encapsulated nucleic acids.

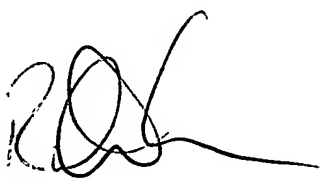
Applicant submits at page 12 that the Office's contention that one would have been motivated to use the method of Kirby because it provided excellent encapsulation yields is a hindsight justification which is not supported by either reference. This is unpersuasive because the method of Kirby resulted in a DNA encapsulation efficiency of 72% +/- 8.5%. See Table 1. This is objective evidence of excellent encapsulation yield. Furthermore, the method of Kirby has the advantages of being simple and mild. See title, page 979; column 1, lines 5-8 of second paragraph; Table I on page 980., and page 982, column 2, lines 1-3 of second full paragraph. Thus one would clearly have been motivated to use it to encapsulate nucleic acids for preparation of DNA vaccines.

Applicants arguments at page 12 indicating that there is nothing in the cited references regarding generating a cell based and humoral immune response is unpersuasive. The claimed methods steps are obvious for the reasons set forth in the rejection, and the nature of the produced immune response is considered to be an inherent result of the steps.

At page 13, Applicant asserts that the combination of references is improper because the cationic lipids of Felgner are used to form complexes with nucleic acids in which the nucleic acid is ionically bound to a preformed liposome, and not entrapped in the intravesicular space. This is unpersuasive for two reasons. First, Felgner does fairly teach a method of entrapping nucleic acids into the intravesicular space of liposomes. See column 15, lines 7-20 which clearly teaches encapsulation of bioactive agents into the lumen of liposomes. It is clear from the disclosure of Felgner as a whole that nucleic acids are considered to be bioactive agents, see e.g. abstract column 1,

lines 12-18, column 2, lines 7-11, and column 4, lines 10-14. Second, it would have been obvious to encapsulate the nucleic acids within the intravesicular space in order to protect the nucleic acids from nucleases, thereby increasing the stability of the nucleic acids in vivo. Applicant argues at page 14 that any basis for asserting that the loss of solutes from the multilamellar vesicles of Kirby would correlate with increased protection from nucleases, relative to that provided by unilamellar liposomes, lacks support in fact or logic. In support, Applicant argues that there is no disclosure that nucleases attack nucleic acids. This is unpersuasive because it is clear to one of ordinary skill in the art from the name "nucleases" that the activity of these enzymes is to attack and degrade nucleic acids. Applicant states that there is no basis for asserting that nucleases diffuse into liposomes, and notes that the carboxyfluorescein observed by Kirby to diffuse through liposomal membranes is very different from nucleases. This is unpersuasive. Kirby indicates at page 982, column 1, lines 4-8 that multilamellar liposomes, rather than unilamellar liposomes, should afford maximum protection against the effects of enzymes. Thus it is clear that those of ordinary skill in the art, aware of Kirby would have thought that multilamellar liposomes provided more protection against enzymes, including nucleases, than would unilamellar liposomes.

For these reasons the rejections are maintained.



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PRIMARY EXAMINER